

## **II. LISTING OF CLAIMS**

The listing of claims will replace all prior versions, and listings, of claims in the application:

Claims 1-7. (Cancelled)

Claim 8. (Previously Presented) A method of effectively treating seasonal allergic rhinitis, chronic idiopathic urticaria, or both conditions in a human patient, comprising administering loratadine transdermally to the human patient by applying a transdermal delivery system comprising (i) an active agent consisting of loratadine or a pharmaceutically acceptable salt thereof, (ii) a polymer, (iii) a softening agent; and (iv) a solvent, to the skin of a patient, and maintaining said transdermal delivery system in contact with the skin of the patient for at least 5 days, said transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of said loratadine within three days from the initiation of the dosing interval, and thereafter maintaining a therapeutic blood level until the end of at least the five-day dosing interval, said transdermal delivery device maintaining a plasma level of loratadine at steady state of about 3 ng/ml;

said transdermal delivery system having a mean relative release rate of from about 2.8  $\mu\text{g}/\text{cm}^2/\text{hr}$  to about 16.2  $\mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 24 hours;

from about 2.3  $\mu\text{g}/\text{cm}^2/\text{hr}$  to about 13.7  $\mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 48 hours;

from about 2.0  $\mu\text{g}/\text{cm}^2/\text{hr}$  to about 11.9  $\mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 72 hours;

and a mean relative release rate of from about 1.8  $\mu\text{g}/\text{cm}^2/\text{hr}$  to about 9.9  $\mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin, said cell having a receptor chamber containing a 40:60 mixture of ethanol:water.

Claim 9. (Original) The method of claim 8 wherein the plasma level of loratadine at 48 hours does not decrease by more than 30% over the next 72 hours.

Claim 10. (Original) The method of claim 8, further comprising maintaining an effective mean relative release rate of said transdermal delivery system to provide a substantially first order plasma level increase of loratadine from the initiation of the dosing interval until about 48 to about 72 hours after the initiation of the dosing interval; and thereafter providing an effective mean relative release rate to provide a substantially zero order plasma level fluctuation of loratadine until the end of at least the five-day dosing interval.

Claim 11. (Original) The method of claim 8, further comprising providing a mean relative release rate of loratadine from said transdermal delivery system to provide a plasma level of loratadine of at least about 0.1 ng/ml within about 6 hours after application of said transdermal delivery system onto the skin of the patient.

Claim 12. (Cancelled)

Claim 13. (Original) The method of claim 8, wherein said therapeutic plasma level is maintained from about 0.1 ng/ml to about 3.3 ng/ml during the dosing interval for said transdermal delivery system.

Claim 14. (Original) The method of claim 8, wherein said transdermal delivery system has a mean relative release rate from about 1.0  $\mu\text{g}/\text{hour}/\text{cm}^2$  to about 30.0  $\mu\text{g}/\text{hour}/\text{cm}^2$ .

Claim 15. (Cancelled)

Claim 16. (Previously Presented) The method of claim 8, wherein said transdermal delivery system provides an in-vitro cumulative amount of permeation of from about 63  $\mu\text{g}/\text{cm}^2$  to about 388  $\mu\text{g}/\text{cm}^2$  of the transdermal delivery system surface area at 24 hours; from about 105  $\mu\text{g}/\text{cm}^2$  to about 660  $\mu\text{g}/\text{cm}^2$  of the transdermal delivery system surface area at 48 hours; and from about 139  $\mu\text{g}/\text{cm}^2$  to about 854  $\mu\text{g}/\text{cm}^2$  of the transdermal

delivery system surface area at 72 hours; and from about  $162 \mu\text{g}/\text{cm}^2$  to about  $955 \mu\text{g}/\text{cm}^2$  of the transdermal delivery system surface area at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and said cell has a receptor chamber containing a 40:60 mixture of ethanol:water.

Claims 17-19 (Cancelled)

Claim 20. (Previously presented) A transdermal delivery system comprising (i) an active agent consisting of loratadine or a pharmaceutically acceptable salt thereof, (ii) a polymer, (iii) a softening agent; and (iv) a solvent, the transdermal delivery system provides a mean relative release rate of from about  $2.8 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $16.2 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 24 hours;

from about  $2.3 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $13.7 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 48 hours;

from about  $2.0 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $11.9 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 72 hours; and

from about  $1.8 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $9.9 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and said cell having a receptor chamber containing a 40:60 mixture of ethanol:water; said transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of said loratadine within 36 hours from the initiation of the dosing interval, and a plasma level of loratadine of at least about  $0.1 \text{ ng/ml}$  by about 6 hours after application of said transdermal delivery system onto the skin of a human patient; said transdermal delivery system maintaining a therapeutic blood level until the end of at least a five-day dosing interval and a plasma level of loratadine at steady-state of about  $3 \text{ ng/ml}$ .

Claim 21. (Cancelled)

Claim 22. (Previously Presented) The transdermal delivery system of claim 20, which provides an in-vitro cumulative amount of permeation of from about  $63 \mu\text{g}/\text{cm}^2$  to about  $388 \mu\text{g}/\text{cm}^2$  of the transdermal delivery system surface area at 24 hours; from about  $105 \mu\text{g}/\text{cm}^2$  to about  $660 \mu\text{g}/\text{cm}^2$  of the transdermal delivery system surface area at 48 hours; and from about  $139 \mu\text{g}/\text{cm}^2$  to about  $854 \mu\text{g}/\text{cm}^2$  of the transdermal delivery system surface area at 72 hours, as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and said cell has a receptor chamber containing a 40:60 mixture of ethanol:water.

Claim 23. (Original) The transdermal delivery system of claim 20, comprising a backing layer which is impermeable to the active substance, a pressure-sensitive adhesive reservoir layer, and optionally a removable protective layer, the reservoir layer by weight comprising 20 to 90% of a polymeric matrix, 0.1 to 30% of a softening agent, 0.1 to 20% of loratadine base or of a pharmaceutically acceptable salt thereof and 0.1 to 30% of a solvent for the loratadine or salt thereof.

Claim 24. (Original) The transdermal delivery system of claim 20, which is a laminated composite comprising (a) a polymer backing layer that is substantially impermeable to loratadine or the pharmaceutically acceptable salt thereof; and (b) a reservoir layer comprising an acrylate or silicone based pressure-sensitive adhesive, 0.1 to 20% of loratadine base or of a pharmaceutically acceptable salt thereof, 0.1 to 30% of an ester of a carboxylic acid acting as a softening agent and 0.1 to 30% of a solvent for loratadine having at least one acidic group.

Claims 25-28. (Cancelled)

Claim 29. (Previously Presented) The transdermal delivery system of claim 20, wherein said therapeutic plasma level is maintained from about 0.1 ng/ml to about 3.3 ng/ml during the dosing interval for said transdermal delivery system.

Claim 30. (Previously Presented) The transdermal delivery system of claim 20, wherein said transdermal delivery system has a mean relative release rate from about 1.0  $\mu\text{g}/\text{hour}/\text{cm}^2$  to about 30.0  $\mu\text{g}/\text{hour}/\text{cm}^2$  of the transdermal delivery system surface area.

Claim 31. (Cancelled)

Claim 32. (Previously Presented) The transdermal delivery system of claim 20, wherein said transdermal delivery system provides an in-vitro cumulative amount of permeation of from about 63  $\mu\text{g}/\text{cm}^2$  to about 388  $\mu\text{g}/\text{cm}^2$  of the transdermal delivery system surface area at 24 hours; from about 105  $\mu\text{g}/\text{cm}^2$  to about 660  $\mu\text{g}/\text{cm}^2$  of the transdermal delivery system surface area at 48 hours; and from about 139  $\mu\text{g}/\text{cm}^2$  to about 854  $\mu\text{g}/\text{cm}^2$  of the transdermal delivery system surface area at 72 hours; and from about 162  $\mu\text{g}/\text{cm}^2$  to about 955  $\mu\text{g}/\text{cm}^2$  of the transdermal delivery system surface area at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and said cell has a receptor chamber containing a 40:60 mixture of ethanol:water.

Claim 33. (Original) The transdermal delivery system according to claim 23, wherein the backing layer is composed of a flexible material.

Claim 34. (Original) The transdermal delivery system according to claim 23, wherein the backing layer is selected from the group consisting of a flexible material, an inflexible material, and an aluminum foil.

Claim 35. (Previously Presented) The transdermal delivery system according to claim 23, wherein the polymeric matrix is at least one of rubber, a synthetic homo-, co- or blockpolymer, a urethane and silicone.

Claim 36. (Original) The transdermal delivery system according to claim 23, wherein the softening agent is at least one of dodecanol, undecanol, octanol, a glycol and glycanol.

Claim 37. (Original) The transdermal delivery system according to claim 23, wherein the solvent is a monoester of a dicarboxylic acid.

Claim 38. (Original) The transdermal delivery system according to claim 23, wherein the solvent is at least one of monomethyl glutarate and monomethyl adipate.

Claim 39. (Cancelled)

Claim 40. (Original) The transdermal delivery system according to claim 23, wherein by weight the polymer is present in about 55%, the loratadine in about 10%, the solvent in about 10% and the softener in about 15%.

Claim 41. (Original) A transdermal delivery system according to claim 23, wherein the solvent is present in from about 25 to 100% the weight of the loratadine.

Claim 42. (Original) The transdermal delivery system according to claim 23, which also comprises a removable protective layer.

Claim 43. (Original) The transdermal delivery system according to claim 23, wherein the pressure-sensitive adhesive reservoir layer comprises a polymer based on an acrylate, a methacrylate, a silicone compound or a combination thereof.

Claim 44. (Previously Presented) The transdermal delivery system according to claim 23, wherein the softening agent is a medium-chain triglyceride of the caprylic/capric acids of coconut oil.

Claim 45. (Original) The transdermal delivery system according to claim 23, wherein the solvent has at least one acidic group.

Claim 46. (Previously Presented) A method of effectively treating seasonal allergic rhinitis, chronic idiopathic urticaria, or both conditions in a human patient, comprising



administering loratadine transdermally to the human patient by applying a transdermal delivery system containing loratadine or a pharmaceutically acceptable salt thereof to the skin of a patient, and maintaining said transdermal delivery system in contact with the skin of the patient for at least 5 days, said transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of said loratadine within three days from the initiation of the dosing interval, and thereafter maintaining a therapeutic blood level until the end of at least the five-day dosing interval, said transdermal delivery device maintaining a plasma level of loratadine at steady state of about 3 ng/ml;

said transdermal delivery device comprising a backing layer which is substantially impermeable to the loratadine or pharmaceutically acceptable salt thereof; and a reservoir layer consisting essentially of 20 to 90% by weight of a polymeric matrix, 0.1 to 30% by weight of a softening agent; 0.1 to 20% by weight of loratadine base or of a pharmaceutically acceptable salt thereof and 0.1 to 30% by weight of a solvent, for the loratadine or salt thereof;

said transdermal delivery system having a mean relative release rate of from about  $2.8 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $16.2 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 24 hours;

from about  $2.3 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $13.7 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 48 hours;

from about  $2.0 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $11.9 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 72 hours;

and a mean relative release rate of from about  $1.8 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $9.9 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 96 hours ; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin, said cell having a receptor chamber containing a 40:60 mixture of ethanol:water.

Claim 47. (Previously Presented) The method of claim 8, wherein said transdermal delivery system has a mean relative release rate of from about  $1.5 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $8.5 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 120 hours;

from about  $2.4 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $7.7 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 144 hours;

and from about  $1.5 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $6.7 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 168 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin, said cell having a receptor chamber containing a 40:60 mixture of ethanol:water.

Claim 48. (Previously Presented) The transdermal delivery system of claim 20, wherein said transdermal delivery system has a mean relative release rate of from about  $1.5 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $8.5 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 120 hours;

from about  $2.4 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $7.7 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 144 hours;

and from about  $1.5 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $6.7 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 168 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin, said cell having a receptor chamber containing a 40:60 mixture of ethanol:water.

Claim 49. (Previously Presented) The method of claim 46, wherein said transdermal delivery system has a mean relative release rate of from about  $1.5 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $8.5 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 120 hours;

from about  $2.4 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $7.7 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 144 hours;

and from about  $1.5 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $6.7 \mu\text{g}/\text{cm}^2/\text{hr}$  of the transdermal delivery system surface area at 168 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin, said cell having a receptor chamber containing a 40:60 mixture of ethanol:water.

Claim 50. (Previously Presented): The method of claim 8, wherein a softening agent is selected from the group consisting of dodecanol, undecanol, octanol, a glycol, glycanol and a medium-chain triglyceride of the caprylic/capric acids of coconut oil; and the



solvent is selected from the group consisting of a monoester of a dicarboxylic acid, monomethyl glutarate and monomethyl adipate.

Claim 51. (Previously Presented): The transdermal delivery system of claim 20, wherein a softening agent is selected from the group consisting of dodecanol, undecanol, octanol, a glycol, glycanol and a medium-chain triglyceride of the caprylic/capric acids of coconut oil; and the solvent is selected from the group consisting of a monoester of a dicarboxylic acid, monomethyl glutarate and monomethyl adipate.

Claim 52. (Previously Presented): The method of claim 46, wherein a softening agent is selected from the group consisting of dodecanol, undecanol, octanol, a glycol, glycanol and a medium-chain triglyceride of the caprylic/capric acids of coconut oil; and the solvent is selected from the group consisting of a monoester of a dicarboxylic acid, monomethyl glutarate and monomethyl adipate.

Claim 53. (Previously Presented): The method of claim 8, wherein the transdermal delivery system comprises a solution of the loratadine or a pharmaceutically acceptable salt thereof.

Claim 54. (Previously Presented): The transdermal delivery system of claim 20, wherein the transdermal delivery system comprises a solution of the loratadine or a pharmaceutically acceptable salt thereof.

Claim 55. (Previously Presented): The method of claim 46, wherein the transdermal delivery system comprises a solution of the loratadine or a pharmaceutically acceptable salt thereof.